Our new meta analysis is published

Mistletoe therapy is popular among patients in German-speaking countries as an adjunct treatment for cancer. This is due to the fact that Ita Wegmann, an associate of Rudolf Steiner, had introduced mistletoe into medical cancer therapy at his suggestion. Steiner used, besides the knowledge of old European healing traditions, mainly his intuition and the mistletoe's signature: mistletoe grows parasitically on trees and feeds on the host tree, which slowly but surely perishes. So according to the ancient signature theory and its phenomenology, mistletoe should also work on humans for a similar disease, namely cancer, which is also a parasitic growth in the body.

Early studies

In the 1970s and 1980s, much basic research was done on mistletoe extracts. This showed that mistletoe contains an abundance of immunologically relevant substances, so-called lectins, which activate the immune system [1]. At that time, the first clinical studies began, in which physicians – especially those with an anthroposophical orientation – used mistletoe therapeutically in cancer patients. Initially, this was often done in rather severe cases with terminal cancer. Since then there has been a whole series of investigations. In 2020, my colleague Thomas Ostermann published in our journal *Complementary Medicine Research* a meta-analysis of all clinical trials in which a particular fermented mistletoe preparation, Iscador, had been used with all kinds of cancer types and in which survival was measured [2]. This publication was an update of a previously published study and included new studies, for a total of 32, both randomized and non-randomized comparative studies. The hazard ratio was 0.59, pretty much the same as in the earlier analysis.

The hazard ratio quantifies the difference between treatment group and control group (mostly normal treatment) over time. In this case, it means that patients treated with Iscador are 41% more likely to survive longer, meaning they live significantly longer. (It is not possible to estimate how long patients live longer overall in such analyses because observation durations vary widely. Therefore, one can only gain an estimate of the probability of living longer and a hedge on whether that probability is more than a random fluctuation.)

Our previously published analyses

Last year, we had extended Ostermann and colleagues' analysis to non-fermented mistletoe extracts [3]. Indeed, mistletoe extracts can be fermented or prepared as a simple extract,

and depending on this, clinical experience tells us that the effect is different. In our analysis, we also found a significant effect size of mistletoe extracts on survival, but slightly smaller, with a hazard ratio of 0.81. Thus, the probability of survival with non-fermented mistletoe extracts is 19% higher than without.

Mistletoe therapy is often used in addition to conventional drugs with the aim of improving quality of life. We pursued this question in our first analysis [4]. Quality of life is measured with questionnaire instruments and is therefore metric. This means one must also use other summary measures, in this case the standardized mean difference (or SMD) „d".

We found a joint effect size of d = 0.61 in this first analysis of mistletoe on quality of life in cancer patients. The effect size measure d is a dimensionless quantification of an effect independent of sample size and measured scale, and expresses the effect in standard deviations (because the mean difference is divided by the standard deviation, i.e., standardized; hence, „standardized mean difference").

For reference, remember: effects below d = 0.3 are considered small. Those between 0.3 and 0.6 as medium, and those above 0.6 as large. For example, if one examines the effects of psychotherapy on all possible disorders, one often gets effects between 0.6 and 0.8. The English regulator NICE often calls for effects greater than 0.5, that is, greater than half a standard deviation difference.

Our new analysis

We have now narrowed this earlier analysis to look only at studies that measured quality of life in breast cancer treated with mistletoe therapy, adding a more recent study. We did this because both Thomas Ostermann and we ourselves saw that breast cancer patients made up the largest proportion of studies, or studies on breast cancer patients, on the one hand, make up the largest proportion of studies, and on the other hand, usually yield better results than, for example, in lung cancer patients. Thus, one can assess the study situation more homogeneously.

Our new study was published in the journal *Integrative Cancer Therapies* as well [5]. It has now been online for a few days. We included nine randomized and seven non-randomized comparative studies. We again found an effect size of d = 0.61 across all randomized trials. This was smaller for the non-randomized trials: d = 0.46. This may be because some of the non-randomized trials included more severely ill patients.

We saw in the sensitivity analysis, which examines how robust the results are, that

1. Patients with tumor stage 1-3 versus those with tumor stage 1-4 had better effects

(namely, d = 0.68 vs. 0.57)
2. Studies that were methodologically better produced higher effects (d = 0.71 vs. d = 0.45) or those that were blinded showed better effects (d = 0.69) than those that were unblinded (d = 0.47)

This makes it unlikely that our results are only due to methodological artifacts.

Mistletoe studies are often criticized for rarely being blinded. Indeed, it is not easy to blind mistletoe studies because mistletoe injection causes local redness, and ethics committees rarely think it is a good idea to use as a comparator injection a placebo that also causes redness but has no other ingredients.

We saw that younger patients tended to have a better effect.

Overall, then, this more recent, more focused analysis also shows that mistletoe preparations improve patients‘ quality of life.

By the way, the study was funded by the „Integrative Medicine & Pharmacy“ foundation in Stuttgart. And for specialists: we extracted the data twice separately, compared them, discussed divergences and calculated the statistical analysis separately with two programs. The results were the same up to two decimal places. This double comparison is relatively important from a methodological point of view. We did not do this in another study, which resulted in a stupid error. I’ll get into that shortly.

I had presented our first analysis during the Corona period at an online conference. Afterwards, the moderator, a professor of general medicine in England asked me in amazement: if mistletoe shows such a clear effect on quality of life, as we have now seen, why is it not used everywhere? That was a good question. My answer was: because medical therapy is only partially based on scientific data, and most of it is politics. That is what I had to painfully learn in my more than 30 years as a researcher.

Despite this, I hope that our data will help mistletoe therapy, which is obviously useful, to be better accepted and more widely used. Because it obviously helps patients. We will see if this will also be the case in England. The English are currently planning their first large randomized mistletoe study in general practice. A unique one, including only English people…

Sources and literature

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